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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,692	10/19/1999	JEFFREY M. BESTERMAN	106.101.197	3139

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EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 05/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/420,692	BESTERMAN ET AL.	
	Examin r	Art Unit	
	Janet Epps	1635	

-- The MAILING DATE of this communication appears on th cover sheet with the corr spondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-41 and 46-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-41 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (Claims 1-6, 11-41, and 46-50, wherein said gene encodes a DNA methyltransferase) in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicants canceled claims 7-10 and 42-45. Claims 1-6, 11-41, and 46-50 are currently pending in the instant application.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 14, 16, and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Ju et al. Claims 1, 14, 16, and 22-23 read on a method for inhibiting the expression of a gene in a cell comprising contacting the cell with an effective synergistic amount of an antisense oligonucleotide, which inhibits expression of the gene, and an effective synergistic amount of a protein effector of a product of the gene.

Ju et al. teach a method for inhibiting the expression of the thymidylate synthase (TS) gene in KB31 cells. The method of Ju et al. comprises administering to said cells an antisense construct that produces antisense that inhibits the expression of TS mRNA, in combination with an inhibitor of the TS protein product, wherein said inhibitor is 5-fluoro-uridine (FdUrd, page

125: Figure 43). The results of the experiment demonstrated that KB31 cells transfected with the TS antisense vector were more sensitive to FdUrd compared to control vector treated cells. Furthermore, the results of Ju et al. demonstrate that decreasing TS protein levels in cells using the antisense approach resulted in a "synergistic" enhancement in the cytotoxicity of FdUrd (Figure 43, and page 130, Summary).

Ju et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 38-41, 46, 48-50 are rejected under 35 U.S.C. 102(a) as being anticipated by Szyf et al. (WO 97/44346), as evidenced by Szyf et al. (US Patent 5,578,716)

Claims 38-41 and 46 and 48 read on an inhibitor of a gene comprising an antisense oligonucleotide, which inhibits expression of a gene in operable association with a protein effector of a product of the gene. Although the term "operable association" is considered unclear, for prior art purposes the term is interpreted to encompass antisense oligonucleotides in association with nucleoside or nucleotide type protein effectors by means of phosphate ester type linkages. Additionally, claims 49-50 recite pharmaceutical compositions comprising said inhibitor. For prior art purposes, the term pharmaceutical is considered an "intended use" limitation, and therefore is not considered to hold any patentable weight since the limitation is not deemed necessary to breathe life or meaning into the claim. Therefore, for search purposes a

composition comprising the inhibitors of the instant claims in combination with a carrier for delivery into cells will be considered to anticipate the claimed invention.

Szyf et al. disclose DNA MeTase inhibitors, wherein said inhibitor comprises an antisense oligonucleotide portion that inhibits the expression of the DNA MeTase gene (see page 17, lines 27-30, region "X" in the general structure recited at the bottom of the page). Additionally, towards the 3' region of the inhibitor, the "B" region in the structure of the inhibitor can be substituted with a cytosine, inosine, uridine, 5-bromocytosine or 5-fluorocytosine, wherein the "B" region and about 2 flanking nucleotides of the inhibitor are deoxyribonucleosides (page 10, lines 10-19; therefore the "B" region preferably comprises 2'-deoxyribonucleosides). See, for example, SEQ ID NO: 28, which comprises a 5'-fluorocytosine ("F", see page 14, line 40). The sequence C-A-T-C-T-G-C-C-A-T-T-C-C-C-A-C-T-C-T-A set forth in SEQ ID NO: 28 is disclosed in the prior art as a known antisense inhibitor of the DNA MeTase gene (see Szyf et al. US Patent 5,578,716, SEQ ID NO: 1). Furthermore, the hairpin portion of the inhibitors (see SEQ ID NO: 28, page 13, lines 50-51) of Szyf et al. also function as a powerful mechanism based inhibitor of the DNA MeTase enzyme (page 9, lines 28-34).

The oligonucleotide inhibitors of Szyf et al. encompasses polymers of two or more deoxyribonucleotide, ribonucleotide or 2'-O-substituetd ribonucleotide monomers or a combination thereof (page 15, lines 1-4). In certain preferred embodiments of the Szyf et al. invention, the internucleoside linkages of the oligomeric inhibitors may be phosphodiester, phosphotriester, phosphorothioate or phosphoramidate linkages, or combinations thereof (lines 6-9). Additionally, the inhibitors of Szyf et al. may optionally be formulated with any of the well-known pharmaceutically acceptable carriers or diluents (page 17, lines 20-26).

Szyf et al., teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4-6, 11-14, 16, 18, 20, 22-26, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of a gene in a cell *in vitro* and in xenograft tumor cells in an experimental mouse model *in vivo* does not reasonably provide enablement for inhibiting the expression of a gene *in vivo* for the therapeutic treatment of mammals broadly, an in particular a human, having a disease associated with the expression of said gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims read on a method for inhibiting the expression of a gene in a cell comprising contacting the cell with an effective synergistic amount of an antisense oligonucleotide, which inhibits expression of the gene, and an effective synergistic amount of a protein effector of a product of the gene. The instant method encompasses inhibiting the expression of a gene in a cell, wherein said cell is *in vitro* or *in vivo*. However, the specification as filed fails to provide sufficient guidance and/or instruction to practice the full scope of the claimed invention, particularly wherein said method encompasses an *in vivo* method for the

therapeutic treatment of a mammal broadly, including a human, having a disease associated with the expression of a gene, for the reasons set forth in the rejection below.

9. Claims 2-6, 11-13, 15, 17, 19, 21, 27-31, 35-37 and 49-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting xenograft tumor growth in an experimental mouse model *in vivo*, does not reasonably provide enablement for *in vivo* treatment of established tumors or diseases responsive to inhibition of a gene in mammals broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 2, and those claims dependent thereon, recite a method for treating a disease responsive to inhibition of a gene in a mammal comprising administering to a mammal, including a human, which has at least one cell affected by the disease present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and a therapeutically effective synergistic amount of a protein effector of a product of the gene.

Claim 3, and those claims dependent thereon, recite a method for inhibiting tumor growth in a mammal, including a human, comprising administering to a mammal, including a human, which has at least one neoplastic cell present in its body, a therapeutically effective synergistic amount of an antisense oligonucleotide which inhibits expression of a gene involved in tumorigenesis, and a therapeutically effective synergistic amount of a protein effector of a product of the gene. The antisense oligonucleotide in each method may be in operable association with a protein effector, wherein the gene in the claimed method encodes a DNA

methyltransferase, and wherein the protein effector is selected from the group consisting of 5-aza-2'-deoxycytidine, 5-fluoro-2'-deoxycytidine, and 5,6-dihydro-5-azacytidine.

In the instant case it is concluded that the amount of experimentation required to practice the full scope of the claimed invention would be undue based upon the following considerations. The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The specification as filed provides multiple *in vitro* examples wherein Applicants successfully demonstrated the efficacy of antisense oligonucleotides targeting the DNA methyltransferase gene in combination with a protein effector such as 5-aza-dC (5'-aza-2'-deoxycytidine) to inhibit the expression of a gene, and further to inhibit cancer cell growth (see for example Figure 20A). Additionally, the specification as filed discloses a working example of *in vivo* treatment of human tumor cells with a particular antisense oligonucleotide targeting human DNA methyltransferase (MeTase), MG98, in combination with the MeTase protein effector 5-aza-dC. Example 6, page 53, describes treatment results in the inhibition of experimental tumor growth following xenograft inoculation of human colon cancer cells into a mouse model of experimental human tumor cell growth and experimental metastases. Tumor growth inhibition was only demonstrated with the combination of the antisense MG98 and 5-aza-dC. When the antisense oligonucleotide was administered alone, there was an actual *increase* in tumor volume. In contrast, administration of 5-aza-dC alone, showed a marked reduction in

tumor volume. The specification further discloses that administration of the specific combination of MG98 and 5-aza-dC resulted in a synergistic reduction in tumor volume (see Figure 20, X). However, Applicants have not demonstrated that the actual synergistic reduction in tumor volume is actually associated with antisense inhibition of gene expression; Applicants' results are potentially the result of an unknown and unexpected "non-antisense" effect (see discussion below of Crooke, 1998) of the oligonucleotide MG98.

The instant claims recite wherein the antisense oligonucleotide used in the claimed amount must be administered to or contacted with the cells to be treated, in a "effective synergistic amount." The specification as filed does not provide sufficient guidance that would allow one of skill in the art to determine what this "effective synergistic amount" of said antisense oligonucleotide is without undue experimentation. One of skill in the art would have to resort to determine, *de novo*, the *in vivo* ability of an antisense oligonucleotide to interact synergistically with a protein effector in a mammal, prior to practicing the claimed invention. In light of the level of unpredictability associated with the antisense oligonucleotide therapy art (see below), coupled with the lack of guidance provided in the specification as filed, particularly as applied to practicing the generic methods of claims 1-3 (i.e. no specific antisense compound, protein effector, or gene target is defined in these claims), the amount of experimentation required to practice the instant invention would be undue for the skilled artisan to practice the full scope of the claimed invention.

Moreover, the specification does not provide particular guidance or particular direction for the inhibition of DNA MeTase expression, particularly with regard to the treatment of cancers, including metastatic tumors, in the whole mammal comprising the administration of

antisense oligonucleotides in combination with a protein effector. As stated above, the first step in each method requires that the skilled artisan contacts or administers to a cell, an "effective synergistic amount" of an antisense oligonucleotide, which inhibits expression of the target gene. However, the specification does not provide guidance for the delivery of antisense compounds into the diseased tissues of any mammal, in quantity sufficient to detect the presence of DNA MeTase, and to inhibit DNA MeTase gene expression. The specification provides no particular nexus between the inhibition of experimental tumor induction in mouse models from the pre-implantation of human colon cancer cells and the treatment of any disease responsive to inhibition of a gene or for inhibiting the growth of any tumor, in all mammals, including humans. Particularly, by the *in vivo* administration of any antisense oligonucleotide complementary to a target portion of a DNA MeTase mRNA, or antisense to another undefined gene target, in combination with any protein effector of the product of said gene target. It is also noted that the specification provides no working examples of *in vivo* diagnosis or *in vivo* treatment of established tumors. The specification provides no nexus between the inhibition of tumorigenicity in mice, and the treatment of cancers in any mammal, claimed and as contemplated by the specification. The specification provides no particular guidance or direction for the diagnosis or treatment of any cancer in any mammal using the antisense oligonucleotide of the claimed invention in combination with a protein effector.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful

consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with

cellular proteins can render target sites totally inaccessible *in vivo*. Moreover, Branch states "[h]owever, their *(antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells*, Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (See page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention, particularly to determine the *in vivo* "effective synergistic amount" of an antisense oligonucleotide to be used in combination with a protein effector, would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a

disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining the structures of target genes, wherein a disease state is responsive to inhibition of said gene. Next, the skilled artisan would be required to identify antisense oligonucleotides that are capable of inhibiting the expression of said gene *in* vivo, and further determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (i.e. treatment of the disease condition) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

10. Claims 1-6, 11-41 and 46-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a. Claims 1-6, and 11-37 are drawn to methods comprising administering to a mammal, or contacting a cell with an "effective synergistic amount" of antisense oligonucleotide which inhibits the expression of a gene, and an "effective synergistic amount" of a protein effector of a product of said gene, including wherein said gene encodes a DNA methyltransferase. It is noted that claim 1 does not recite a specific gene target.

b. Claims 38-41, and 46-50 are drawn to an inhibitor of a gene comprising an antisense oligonucleotide, which inhibits expression of the gene in operable association with a protein

effector of a product of the gene, modified antisense, and compositions comprising said antisense; wherein the antisense oligonucleotide is in operable associated with two or more protein effectors; and further including wherein said gene encodes a DNA methyltransferase (DNA MeTase).

First it is noted that the specification as filed does not provide sufficient guidance for the skilled artisan to predict what is an "effective synergistic amount" of either an antisense oligonucleotide or protein effector. The skilled artisan prior to practicing the claimed invention must empirically determine these parameters. Claims 1-3 and 38, for example, are not limited to a specific gene target, therefore these claims read on any gene target, including all allelic and polymorphic variants from all organisms. Claims 5-6, 26, and 40, for example recite wherein the gene target is a DNA MeTase. However, since the claims are not limited to a specific structural species of DNA MeTase, these claims encompass DNA MeTase from all species of organisms, including all polymorphic, allelic, mutated, and splice variants of DNA MeTase.

The specification provides only antisense compounds complementary to target sites of the sequence according to GenBank Accession No. X63692, which corresponds to the human DNA Methyltransferase (DNA MeTase) gene. However, the description of these antisense oligonucleotides are not sufficient to predict the structures of antisense oligonucleotide effective to inhibit the expression of all allelic, polymorphic, mutated, and splice variants of the mRNA encoding human DNA MeTase. Due to variations in mRNA folding as it relates to variations in nucleotide sequence, absent evidence to the contrary, variants of DNA MeTase mRNA could potentially possess distinct tertiary structures from that possessed by the mRNA corresponding to GenBank Acc. No. X63692, that would inherently possess distinct intracellular accessible sites

for antisense compounds to bind and effectively inhibit human DNA MeTase expression. According to Branch (1998), "RNAs are complex molecules with intricate internal structures...[r]ecent studies emphasize the extent to which native RNA structure restricts the binding of ODNs *[oligonucleotides]*....[t]hey found that 'surprisingly few' ODNs bound stably to the mRNA, and concluded that binding is probably 'confined to those regions in the RNA which provide an accessible substructure.'" (page 49, col. 1, paragraphs 2-3). Additionally, Branch (1998) state that "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells." (page 49, col. 1, paragraph 3). Since the state of the antisense art indicates the necessity for empirical studies in order to determine effective antisense compounds, one of skill in the art would not accept on its face that antisense oligonucleotides effective to inhibit the expression of one mRNA target, would be effective to inhibit the expression of all polymorphic, allelic, mutated and splice variants of said mRNA target.

The specification as filed, does not provide sufficient description that would allow one of skill in the art to use empirical studies designing antisense compounds targeted to GenBank Acc. No. X63692 to predict the structures of all antisense compounds effective to inhibit expression of human DNA MeTase mRNA isolated from all polymorphic, allelic and splice variants of this gene.

See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the

claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, "[t]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-6, 11-41 and 46-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the present instance, claims 2-3, and those claims dependent thereon, recite the broad recitation "mammals", and the claim also recites, "including human" which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claims 1-3, and those claims dependent thereon, recite the limitation "effective synergistic amount." Additionally, claims 14-17, recites the limitation "effective period of time," this limitation is also a relative term. However, the terms " effective synergistic amount," and "effective period of time" in the instant are relative terms, which render the instant claims

indefinite. The terms "effective synergistic amount" and "effective period of time" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The limitations "effective synergistic amount" and "effective period of time" are relative to the gene targeted in each method, and the type of disease that is responsive to inhibition of said gene. Moreover, if the target was known, one of skill in the art, absent extensive experimentation, would not know what is an effective or synergistic amount of the antisense oligonucleotide or protein effector to be used for an "effective period of time" in the claimed methods.

Claim 38, line 2, and those claims dependent thereon, recite the phrase "inhibits expression the gene." This phrase is vague and indefinite since the meaning of this phrase within the context of the claim is uncertain. Perhaps, Applicants intended the phrase to recite "inhibits expression of the gene."

Claim 38, and those claims dependent thereon, recite the limitation "in operable association with a protein effector." This limitation is vague and indefinite since it is unclear how the effector is to be structurally associated with the antisense oligonucleotide to render the "association" between the two elements (i.e. protein effector and antisense) "operable." The phrase "in operable association with a protein effector" is a relative term, since it appears that the operability of the association would be dependent upon the relative nature of the antisense oligonucleotide and the protein effector.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 8:30AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps, Ph.D.
Examiner
Art Unit 1635

JLE
May 7, 2002